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Short Communication

Treatment of Advanced Breast Cancer (ABC): The Expanding Landscape of Targeted Therapies

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INTRODUCTION

Breast cancer is the most common cancer in women worldwide with around 1 in 9 women developing breast cancer during their lifetime [1,2]. In the United States of America 230,000 women were diagnosed with breast cancer in 2013 [2]. 16-20% of women present with Advanced Breast Cancer (ABC) and despite improving adjuvant therapies 40% of early breast cancer (EBC) patients will develop metastatic disease [3]. Using current therapies 39,000 women died as a result of their breast cancer in 2013. There is therefore the need to develop and improve therapeutic strategies for the treatment of ABC.

Breast cancer is now recognized as a heterogeneous disease with multiple subgroups with varying molecular signatures. It is this heterogeneity that contributes to the varying prognoses and treatment responses in breast cancer patients [4]. The main recognized subtypes include luminal A and B, and human epidermal growth factor-2 (Her2) (ErbB2) (Figure 1) [5]. Triple negative breast cancers are those that do not belong to these groups and of which 85% show basal-like phenotype (Figure 1). Luminal cancers are positive for the hormone receptors (estrogen and progesterone). Her2 breast cancers show increased Her2 expression via increased gene expression and over-expression of the cell surface receptor. Triple negative breast cancers lack expression of hormonal receptors and Her2. Taking all this together, breast cancer is not a single entity and the challenge is to individualise therapy with the expanding library of molecular targets.

This article will highlight some of the new advances in targeted therapies for the treatment of luminal, Her2-positive and triple negative ABC.

LUMINAL BREAST CANCER (LUMINAL A AND LUMINAL B)

Luminal breast cancer (luminal A and luminal B subtypes) respond to estrogen (hormonal) manipulation. Standard hormonal therapies include tamoxifen, aromatase inhibitors (anastrozole, exemestane and letrozole) and fulvestrant (Figure 2) [6]. Tamoxifen is an anti-estrogen binding to and inhibiting the estrogen receptor. The aromatase inhibitors prevent the conversion of androgens to estrogens in post-menopausal women thus reducing the amount of estrogen available to the estrogen receptor and are either steroidal (exemestane) or non-steroidal in function (anastrozole and letrozole). Fulvestrant binds the estrogen receptor preventing dimerisation and nuclear localization. In the context of ABC, 50% of patients with previously hormonal positive breast cancer fail to respond to hormonal manipulation at relapse. Those that do demonstrate initial responses, relapse in time [6,7]. This may be due to increased hormonal receptor expression, alterations in co-regulator proteins or activation of alternative cell signaling pathways [7]. It is therefore clear that we need to develop newer treatment strategies to overcome this resistance. In terms of hormonal sensitive Her2-positive ABC this can be achieved with simultaneous targeting of both receptors. However, for hormonal sensitive Her2-negative breast cancers, alternative approaches are required.

Increasing evidence suggests that the phosphoinositide-3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway may represent a key step in resistance to hormonal therapies [6,8,9]. AKT and mTOR have been shown to be activated and correlate with poor prognosis in patients receiving hormonal therapy [8]. mTOR inhibition has therefore been investigated in clinical trials (Figure 2). Interim analysis of a phase III (BOLERO-2) trial demonstrated the addition of everolimus to exemestane in the treatment of ABC, resistant to non-steroidal aromatase inhibition, improved disease free survival [10].

Aberrant expression of cell cycle regulators such as cyclin dependent kinase 4/6 (CDK4/6) has been implicated in the development of breast cancer. Breast cancer cell lines representing estrogen receptor-positive luminal breast cancer were highly sensitive to inhibition by palbociclib, a selective CDK4/6 inhibitor (Figure 2). In combination with letrozole, palbociclib, showed promise in pre-clinical and early phase trials

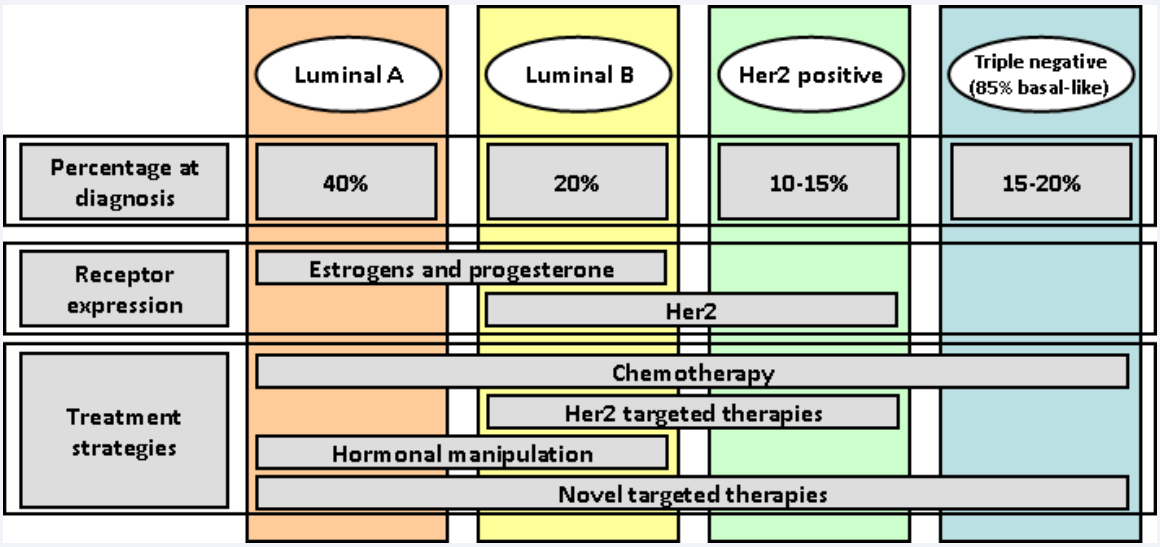

Figure 1 Breast cancer subtypes defined by histology and immunohistochemistry.

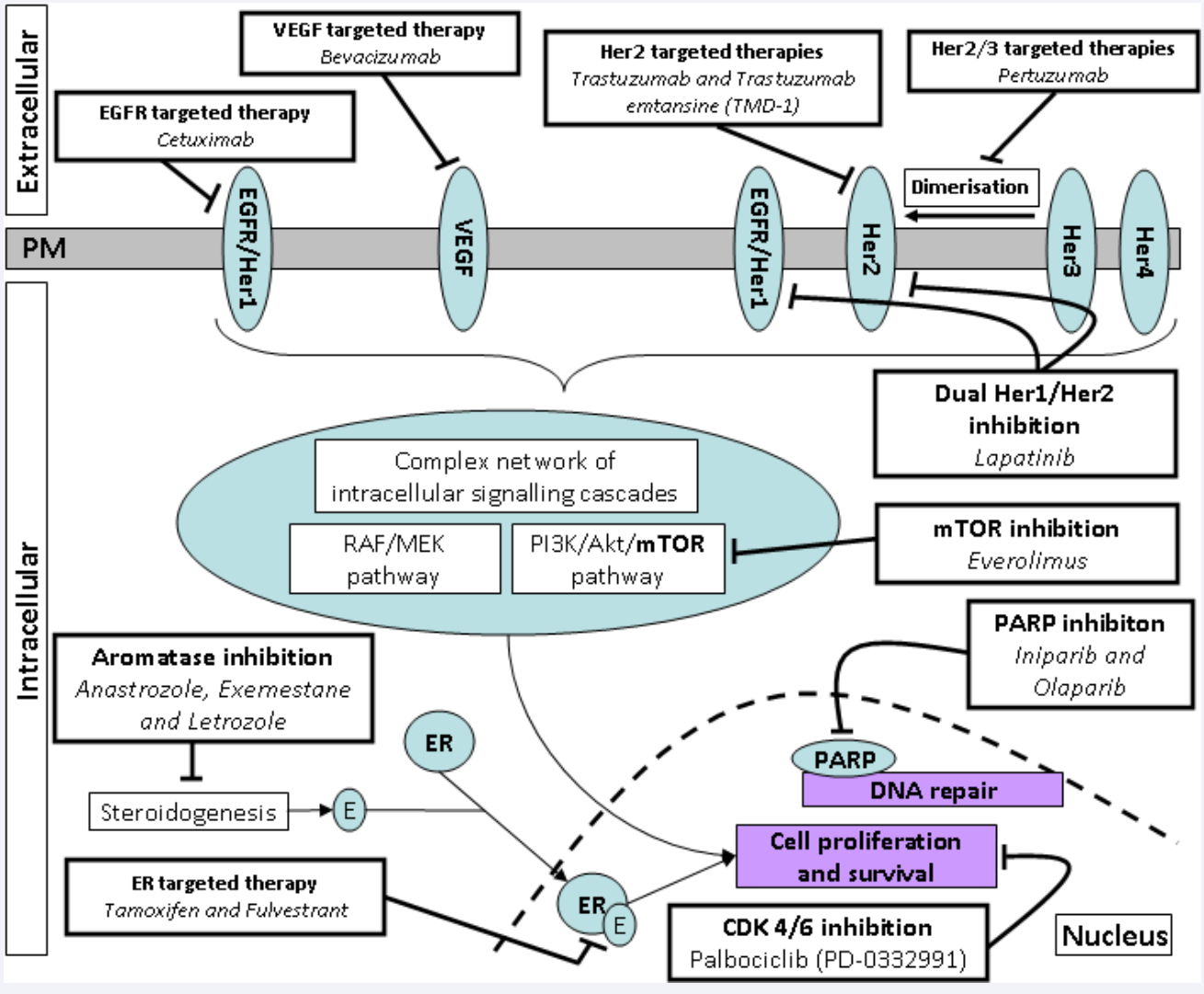

Figure 2 Targeted therapies for the treatment of advanced breast cancer.

[11]. It led to significant improvement in disease free survival when compared to letrozole alone for the treatment of estrogen receptor-positive Her2-negative ABC and a phase III trial (NCT01740427) is currently underway [12].

Her2-positive breast cancer

Her2-positive breast cancers represent approximately 20% of breast cancers and confer a poorer prognosis [13,14]. Her2 targeted therapy with the anti-her2 antibody trastuzumab has improved disease free survival and overall survival in the adjuvant and metastatic setting [15-22]. Unfortunately, there is evidence that Her2-positive ABC becomes resistant to anti-Her2 therapies [23]. Current strategies to overcome resistance include blockade with multiple anti-Her2 antibodies, dual tyrosine kinase inhibitors, and antibody-drug conjugates, alone or in combination (Figure 2).

Her2 targeted antibody combinations have shown efficacy in Her2-positive ABC and provide a potential strategy to overcome resistance to individual Her2 targeted therapies (Figure 2). Pertuzumab binds Her2 and prevents dimerisation with Her3 in a mechanism distinct from that of trastuzumab [24]. The addition of pertuzumab to trastuzumab and docetaxel in treatment of Her2-positive ABC improves disease free survival and overall survival [25].

Dual Tyrosine Kinase Inhibitors (TKI) has demonstrated activity in Her2-positive ABC. The small molecule tyrosine kinase inhibitor lapatinib binds the intracellular domain of the Her1 and Her2 receptor blocking the downstream signaling cascade (Figure 2) [26]. The addition of lapatinib to capecitabine chemotherapy improves disease free survival in Her2-positive ABC [27]. Similarly, lapatinib in combination with letrozole significantly improved disease free survival in Her2-positive ABC compared to letrozole alone [28].

The combination of the antibody trastuzumab and lapatinib has shown promise in the neo-adjuvant setting [29,30]. In ABC, TKI has also shown evidence of greater efficacy, the addition of lapatinib to trastuzumab in patients that have progressed on trastuzumab alone significantly improves overall survival compared to lapatinib alone [31].

There are a number of ongoing trials investigating other combinations of Her2 targeted therapies in Her2-positive ABC [32].

Trastuzumab emtansine (T-DM1) is an antibody–drug conjugate that links the anti-Her2 antibody trastuzumab with DM-1 (derivative of maytansine) allowing direct delivery of a cytotoxic agent to Her2-positive breast cancer cells. TMD-1 has shown good clinical activity in patients with Her2-positive ABC [33-35]. TMD-1 significantly improved both disease free survival and overall survival when compared to lapatinib and capecitabine in patients with ABC previously treated with a taxane and trastuzumab [33].

Resistance to Her2 targeted therapies is likely due to a number of factors, including over-expression of Her2 isoforms, alternative dimerisation, up-regulation of downstream targets and increased ligand binding. Application of the therapeutic strategies described has already demonstrated improvements in patient survival and ongoing clinical trials will further our understanding of resistance to Her2 targeted.

TRIPLE NEGATIVE BREAST CANCER (85% BASAL-LIKE PHENOTYPE)

12 to 17% of breast cancers are triple negative breast cancer (TNBC). TNBC is an aggressive disease lacking any validated therapeutic target [6]. It is defined by the absence of the estrogen receptor, progesterone receptor and Her2 on histology and therefore unresponsive to hormone and Her2 targeted therapies. Eighty-five percent of basal like breast cancer and a high proportion of BRACA mutant (16 to 42%) breast cancers are triple negative [36]. The standard palliative treatment of TNBC remains systemic chemotherapy. TNBC patients initially respond well to treatment but these responses lack durability resulting in a poorer prognosis. There is thus a need to identify new targets for this subgroup.

BRCA1/2 is involved in DNA repair and 16 to 42% of TNBC contain a mutation in the BRCA1/2 gene [36]. This led to the hypothesis that targeting TNBC with DNA damaging agents such as platinum agents will drive cell death as the cells repair machinery is already functionally impaired [37]. A number of phase II studies have been undertaken to determine the efficacy of platinum salts in advanced TNBC demonstrating modest effects and the results of randomized phase III trials are awaited [38-41]. Like BRCA 1/2, Poly (ADP-ribose) polymerases (PARP) plays a critical role in DNA repair. PARP inhibitors have shown promise in breast cancer patients with BRCA1 or BRCA2 mutations [42]. However, the efficacy of PARP inhibitors in unselected patient populations with advanced TNBC has not been confirmed [6].

The role of anti-EGFR targeted therapy in advanced TNBC has also been explored. Cetuximab has demonstrated limited activity as a single agent but in combination with platinum salts may improve anti-tumor activity [41,43]. The efficacy of bevacizumab, the anti-VEGF antibody, in addition to chemotherapy has been studied in advanced TNBC [36]. Retrospective subgroup analysis of the phase III trials (E2100 and AVADO) trials demonstrated improved disease free survival with the addition of bevacizumab to chemotherapy in advanced TNBC with no overall survival benefit [44-46]. However, other similar retrospective analyses failed to confirm this [47].

It is becoming increasingly clear that advanced TNBC is itself markedly heterogeneous. This may account for the varying responses seen to the targeted therapies. Further evaluation of molecular targets is thus underway in this subgroup.

SUMMARY

Breast cancer is the most common cancer in women worldwide [1]. It is becoming clear that the marked heterogeneity in breast cancer spreads beyond those defined by routine histology and immunohistochemistry used for current therapies [48]. In ABC, resistance to current therapies is one of the main therapeutic challenges.. Defining mechanisms of resistance will enable better application of current and development of new therapies to overcome resistance and provide survival gains for the breast cancer patient. In addition, it is clear that breast cancer heterogeneity extends beyond the current subgroups. Therefore

improved understanding of novel molecular differentiators between these groups will drive drug discovery efforts to benefit patient outcomes.

Tumors are grouped into three subtypes that include luminal (A and B), Her2 positive and triple negative breast cancer (85% basal-like phenotype) defined by routine histology and immunohistochemistry. The St Gallen Consensus Conference and European Society of Medical Oncology Guidelines outline these subtypes. The percentage of patients with each subtype at initial diagnosis is shown. The expression of the estrogen, progesterone and Her2 receptor across subtypes is shown. Treatment strategies for each subtype are listed.

The number of targeted therapies for the treatment of advanced breast cancer is expanding rapidly. The figure simplifies the complex network of Plasma Membrane (PM) receptors, intracellular signaling pathways and cellular functions that these therapies target. The main sites for targeting are the extracellular portions of the human epidermal growth factor receptor-1 (EGFR/Her1), Vascular Endothelial Growth Factor (VEGF), human epidermal growth factor-2 receptor 2, 3 and 4 (Her2, Her3 and Her4). Small molecule tyrosine kinase inhibitors target the intracellular domains of Her1 and Her2. These receptors elicit their cellular function by signaling through various intracellular signaling cascades that include the RAF/MEK and PI3K/Akt/mTOR pathway that have also been targets of new therapies. In addition to cell surface receptors and intracellular signaling cascades, novel therapies have targeted nuclear processes, including the cell cycle and DNA repair mechanism. Finally, hormonal manipulation through regulation of Estrogen (E) synthesis and Estrogen Receptor (ER) transactivation remains an important treatment in advanced breast cancer.

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